Advanced Neoplastic Disease

Treatment with 5-Fluorouracil and Irradiation

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• **One hundred and twelve patients with far advanced, inoperable neoplastic disease were treated by a method utilizing the simultaneous administration of the pyrimidine antagonist, 5-fluorouracil, and ionizing irradiation to an estimated tumor dose of 2,000 roentgen units. Seventy-seven of them had periods of objective regression of tumor of three months or more.**

The data presented suggest that either there may be an additive effect when the two modes of therapy are used simultaneously or one mode of therapy may potentiate the antitumor effect of the other.

CURRERI, ANSFIELD and their associates[1,2] have shown that the intravenous administration of the pyrimidine antagonist, 5-fluorouracil (5-FU), produces a significant degree of objective improvement in an impressive number of patients with far advanced cancer. We have confirmed their observations in patients with hepatoma, hormone-resistant carcinoma of the breast and carcinoma of the colon. However, certain kinds of neoplastic disease, particularly squamous cell carcinomas of the lung and of the head and neck, did not respond to treatment with this agent alone.

The studies of Curreri and coworkers also clearly showed that the range between therapeutic and toxic levels of 5-FU administration was narrow, and that pronounced signs of tumor regression were observed when a mild degree of toxicity was induced during treatment with the drug. Major manifestations of toxicity were characterized, most commonly, first by the development of ulcerative lesions in the mucosal lining of the alimentary canal with both squamous and columnar epithelium being affected, and later by suppression of hemopoiesis. Since the growth of normal squamous (or columnar) epithelium was seriously impaired by the administration of 5-FU, it seemed logical to assume that rapidly growing, anaplastic carcinomas of squamous cell origin might absorb enough 5-FU to interfere with the metabolism of individual tumor cells (even though not in a sufficiently high concentration to produce tumor cell death), thus making them more readily susceptible to the cancericidal effects of ionizing radiation. Hence, a study was undertaken to determine the possible response and the toxic effects of 5-FU when administered concomitantly with x-radiation to patients with 5-FU-resistant, inoperable cancers. Preliminary reports of this study have been published.[3,4]

METHOD OF STUDY

The initial phase of this investigation was designed to study the effect of combined therapy on inoperable, anaplastic squamous cell carcinomas of the lung and of the head and neck. Subsequently, other forms of neoplasms, including those in patients with extensive pulmonary metastasis, were included.

The original dosage schedule for 5-FU when used alone, proposed by Curreri and coworkers[1,2] was as follows: 15 mg. per kg. of body weight for five successive days, followed by 7.5 mg. per kg. every third day for four doses. Doses for obese patients were calculated on ideal weight, but no patient, no matter how obese, received more than 1.0 gm. of 5-FU per day. Since it was anticipated that symptoms of toxicity would be produced more readily with combined 5-FU and radiation therapy, a dosage schedule slightly less than that proposed by Curreri and coworkers was adopted by us: 15 mg. per kg. per day was given on three successive days, 7.5 mg. per kg. on the fourth day, the same dose on the fifth day, and thereafter 7.5 mg. per kg. twice weekly until two weeks after x-ray therapy had been completed. The drug was given by intravenous injection. Administration of the compound was interrupted for several days at the first sign of the development of a toxic manifestation. Treatment was resumed as soon as all signs of toxicity had disappeared. Blood cell counts as a rule were obtained at weekly intervals, but occasionally more frequently.

Since it is known that squamous cell carcinomas of the lung and of the head and neck, with rare exceptions, will not regress significantly as a result of irradiation to a depth or tumor dose of 2,000 roentgen units, all of our patients, during the initial phase of this study, received 2,000 r or less total tumor dose concomitantly with the administration of 5-FU. Since it is also known that radiation pneumonitis or

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TABLE 1.—*Results of Treatment with 5-FU + Irradiation (112 Patients with Cancer)*

Type of Neoplasm	No. of Cases	Objective Response	Subjective Response Only	Treatment Inadequate	Not Evaluable	None
Carcinoma:						
Lung	38	33	....	....	....	5
Head, neck	15	10	2	2	1	....
Ovary	8	4	....	1	1	2
Breast	7	5	....	....	....	2
Bladder	5	2	1	....	1	1
Metastasis	5	3	....	....	1	1
Pancreas	4	2	....	....	1	1
Colon, rectum	4	1	1	....	....	2
Stomach	4	2	....	2	....	....
Cervix	4	1	....	1	....	2
Esophagus	3	2	....	....	....	1
Uterus	2	2	....	....	....	....
Gallbladder	1	1	....	....	....	....
Malignant melanoma	4	1	....	....	1	2
Reticular cell sarcoma	3	3	....	....	....	....
Gynandroblastoma	1	1	....	....	....	....
Embryonal cell	1	1	....	....	....	....
Osteosarcoma	1	1	....	....	....	....
Sarcoma, uterus	1	1	....	....	....	....
Mixed tumor, parotid	1	1	....	....	....	....
Total number of cases	112	77	4	6	6	19

pulmonary fibrosis rarely results from a depth dose in the lung of 2,000 roentgen units, the same dosage schedules for irradiation and 5-FU administration were used in patients having extensive pulmonary metastasis as in those with carcinoma of the lung and of the head and neck.

Later in the study, doses of irradiation in excess of 2,000 r (tumor dose) were given when it was felt that the nature and site of the lesion afforded a chance for a prolonged period of palliation. With few exceptions, orthovoltage was used; in a few cases, supravoltage.

In patients with pulmonary lesions, x-ray films of the chest were taken before radiation therapy was begun and one to three weeks after it was completed. Measurements of palpable lesions were made at one or two-week intervals.

RESULTS

The results in this study were reported under these headings: objective response, subjective response, inadequate treatment, not evaluable (result equivocal or patient lost to follow-up), and no response. Objective response includes: (1) measurable reduction in tumor size; (2) leveling off or reversal of downward weight curve; (3) improvement in patient's performance status; and (4) maintenance of the above criteria for a minimum of three months. These criteria are slightly more rigid than those of Curreri and Ansfield, whose data are based on a two months' period of improvement.

The results of combined 5-FU and radiation therapy in 112 patients with cancer are shown in Table 1. Seventy-seven showed improvement that fulfilled the criteria for objective response. The highest incidence of objective response was noted in carcinomas of the lung and of the uterus and in reticular cell sarcoma. Relatively good incidences of response also were observed in carcinomas of the head and neck, esophagus, breast and ovary. In isolated instances, patients with widespread metastasis in the lungs arising from a number of primary sites had long periods of objective response. Illustrative cases are shown in Figures 1 to 7.

TOXICITY

The studies of Curreri and coworkers showed that when 5-FU was used alone, tumor regression was observed only when patients were treated to a toxic level. Therefore, their regimen of therapeutic procedure consisted of an attempt to attain minimal to moderate toxicity yet avoid severe toxicity.

Our protocol was designed to avoid the development of toxic manifestations insofar as possible, although occasional moderate to severe toxic reactions were anticipated because of the apparent additive effect of 5-FU when used concomitantly with ionizing radiation. Toxicity was minimized by careful inquiry daily concerning the earliest symptoms of the development of sore mouth, sore throat, pain on swallowing, cramping abdominal pain or diarrhea. Whenever these symptoms occurred, both radiation and drug therapy were discontinued until the symptoms had abated—three or four days. It was found that failure to follow this practice often resulted in severe toxic reactions. The incidence of toxic manifestations in our series of cases is shown in Table 2.

TABLE 2.—*Toxic Manifestations in Series of 112 Patients with Cancer Treated with Combined 5-FU and X-ray Therapy*

Toxic Manifestations:	No. of Cases
Stomatitis	11
Pharyngitis	7
Dysphagia	9
Nausea and vomiting	4
Diarrhea	19
Loss of hair	3
Dermatitis	2
Leukopenia (below 4,000 cells per cu. mm.)	68
Thrombopenia (below 100,000 cells per cu. mm.)	8

Leukopenia with neutropenia occurred more frequently than any other sign of toxicity. In most instances, the leukocyte count seldom fell below 2,000 to 2,500 cells per cu. mm., but occasionally a severe degree of leukopenia developed with alarming rapidity. In one case, that of a 16-year-old boy who was receiving combined therapy for recurrent squamous cell carcinoma of the nasopharynx that had spread to cervical lymph nodes, the leukocyte count fell from 6,400 to 600 cells per cu. mm. in the course of one week. Treatment was stopped and one week later the leukocyte count had risen to 4,600 cells per cu. mm. In our experience, recovery from a severe degree of leukopenia is almost as rapid as the initial fall, providing both radiation and drug therapy are interrupted promptly.

While combined treatment brought about a decrease in thrombocytes below 100,000 per cu. mm. in eight of 112 patients in the series, hemorrhagic phenomena were not observed. Platelet counts returned to normal levels promptly following cessation of treatment. Erythropoiesis was not significantly affected by the concomitant use of 5-FU and irradiation in the present series.

DISCUSSION

Early studies by Ansfield and Curreri[1] demonstrated that carcinoma of the lung (16 cases) and of the head and neck (four cases) did not respond to treatment with 5-FU when that agent was administered alone. However, in the present study neoplasms of the same type were observed to regress at an unusually rapid rate when treated simultaneously with the drug and ionizing radiation, even with estimated tumor doses as low as 2,000 roentgen units. Moreover, the responses to combined therapy were remarkably consistent. It is postulated that the data herein reported suggest that either there may be an additive effect when the two modes of therapy are used simultaneously or one mode of therapy may potentiate the antitumor effect of the other.

Systemic toxicity from 5-FU does not seem to be enhanced by the concomitant administration of localized irradiation, but mucosal and cutaneous reactions within irradiated fields are decidedly greater with combined therapy than with irradiation alone. This is especially true of pelvic or abdominal fields, necessitating reducing not only individual doses of 5-FU but also the daily doses of radiation (not infrequently by as much as 50 per cent). Except in rare instances of hypersusceptibility, severe toxic reactions can be avoided by carefully inter-

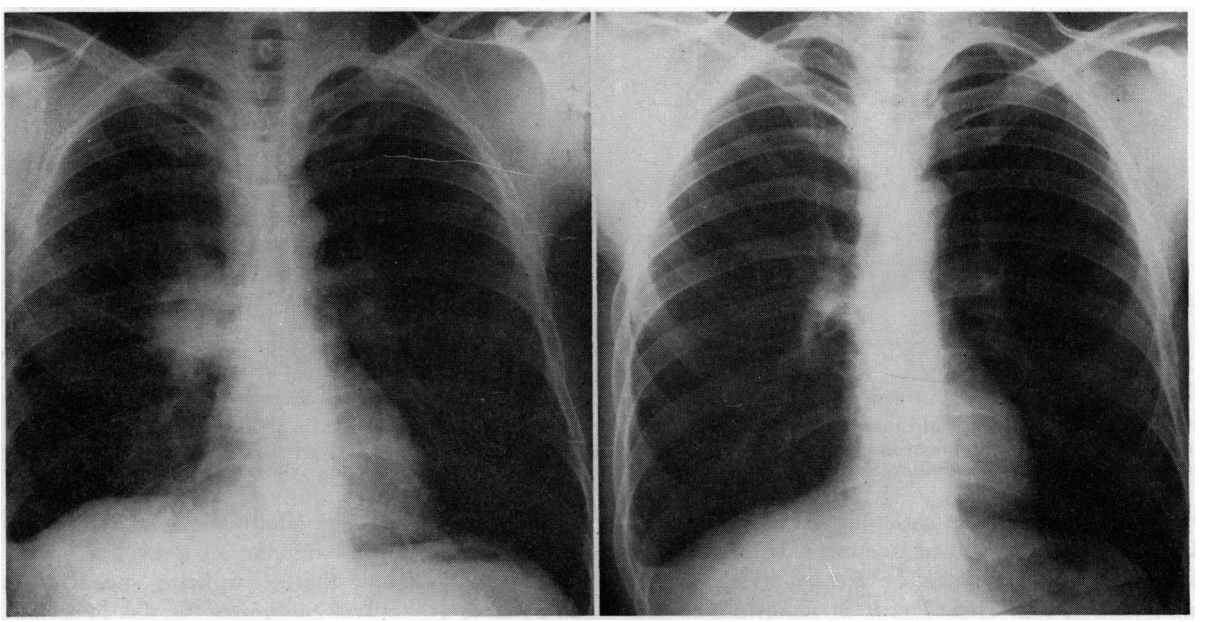

Figure 1.—The patient, a man 44 years old, had bronchogenic carcinoma of the right lung. *Left:* A chest film, dated August 13, 1959, taken before starting combined 5-fluorouracil and orthovoltage radiation therapy. *Right:* Chest film taken on September 15, 1959, four days after completion of combined treatment (estimated radiation tumor dose: 1,890 r).

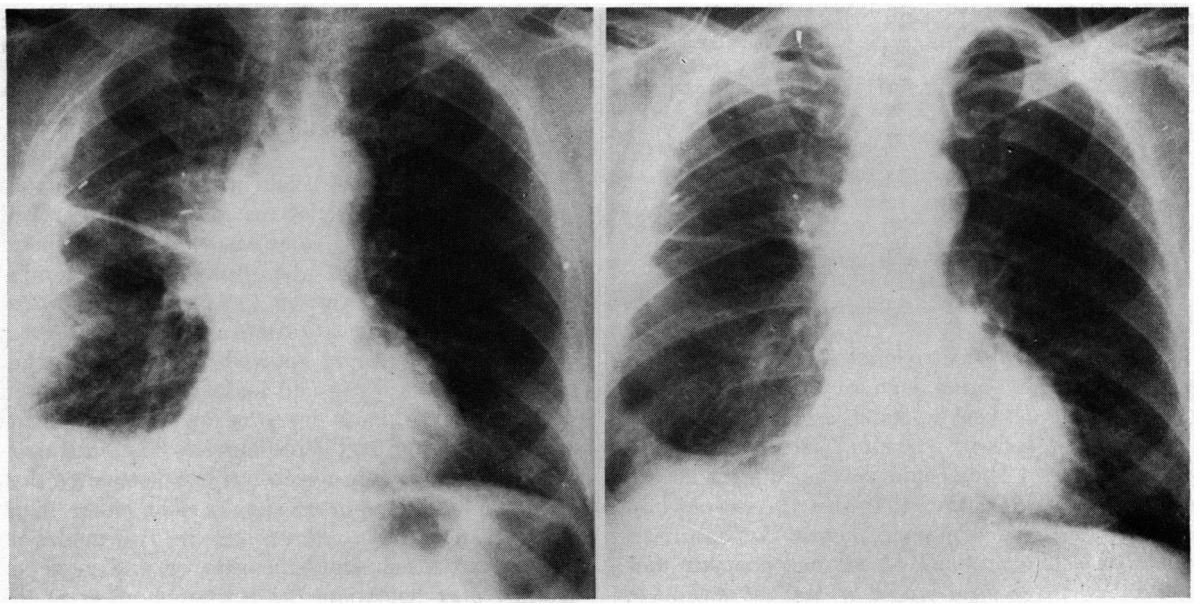

Figure 2.—The patient, a man 70 years of age, had bronchogenic carcinoma, right lung. *Left:* Chest film dated January 19, 1959, taken before commencing combined therapy. Metal clips were inserted to outline tumor margins at time of thoracotomy. *Right:* Chest film dated March 16, 1959 was taken 17 days after completion of supravoltage irradiation (6 MEV linear accelerator), 5,628 rads being delivered into the tumor. The patient was living without evidence of recurrent disease 21 months after institution of treatment.

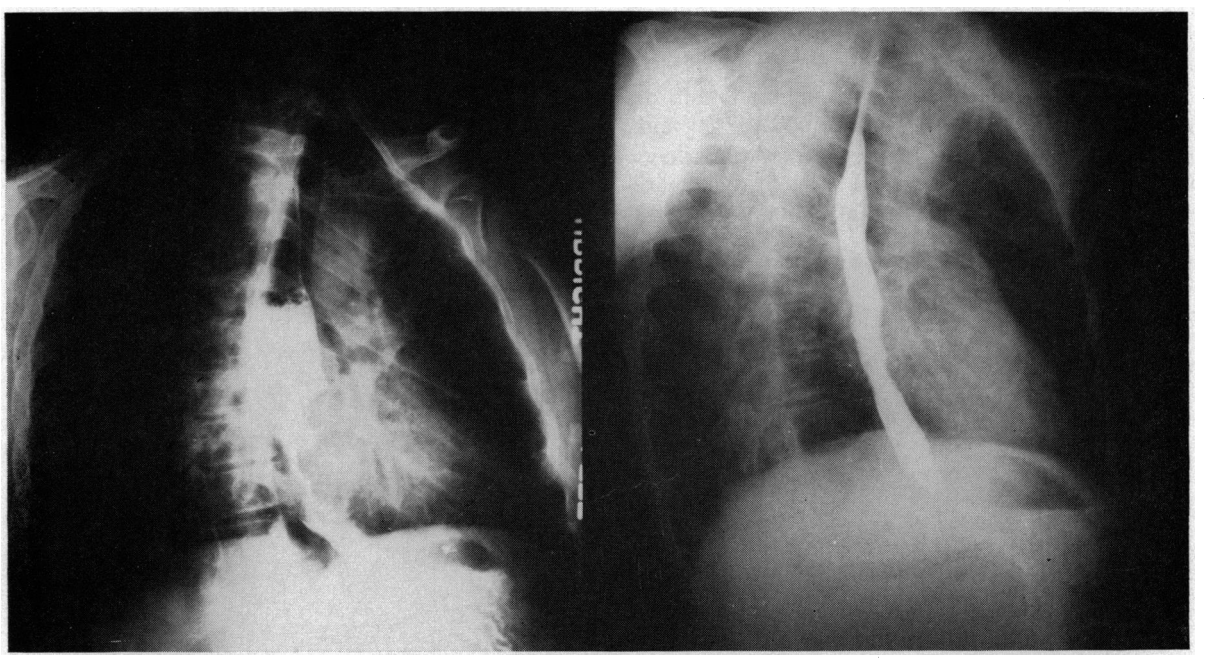

Figure 3.—A 43-year-old man had adenocarcinoma of esophagus at junction of middle and lower thirds. *Left:* Film dated August 18, 1959, taken before starting combined therapy. *Right:* Film dated November 9, 1959 was taken 13 days after completion of irradiation therapy (3,000 r in air delivered to each of two portals, anterior and posterior chest).

viewing and examining patients each day while they are undergoing combined treatment. If this is done, ambulatory patients can be treated safely on an out-patient basis. However, it is important to emphasize that blond or red-headed patients with thin, white skin are particularly susceptible to severe cutaneous reactions when orthovoltage is employed concomitantly with the administration of 5-FU unless the daily dose of irradiation is kept at a very low level. Combined therapy utilizing supravoltage in patients of this type minimizes the risk of serious skin reactions.

At least two advantages to combined therapy of the type described in this paper are readily appar-

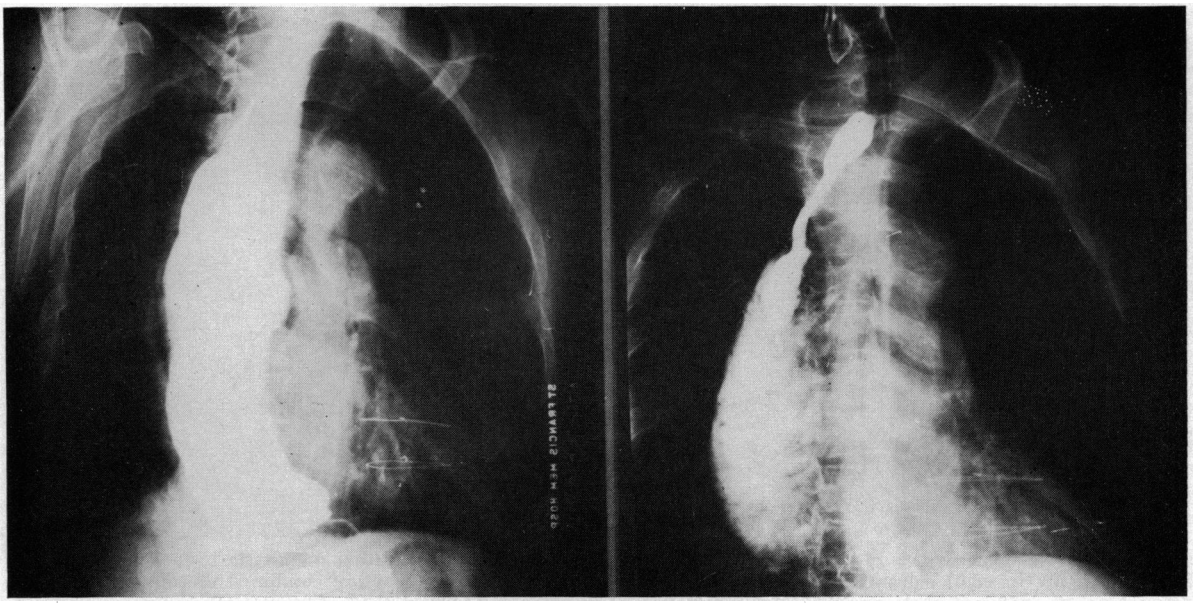

Figure 4.—Case of recurrent squamous cell carcinoma of esophagus at junction of upper and middle thirds in man 68 years of age. *Left:* Film dated July 7, 1960, made before beginning combined therapy, reveals pronounced constriction of the remaining small portion of the esophagus above the transplanted stomach (the lower two-thirds of the esophagus had been resected 1 year previously). *Right:* Film dated August 10, 1960 was made 12 days after completion of irradiation therapy (1,440 r, estimated tumor dose).

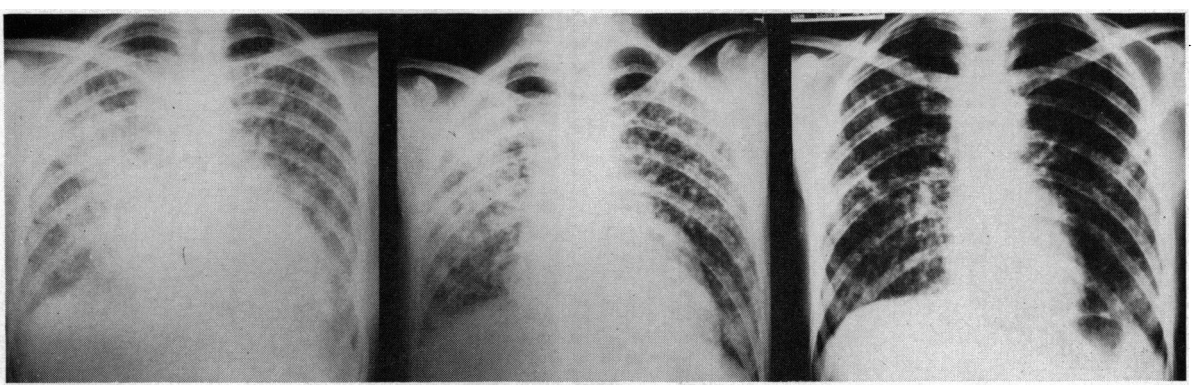

Figure 5.—A woman 28 years of age had widespread metastatic undifferentiated carcinoma, primary site unknown. *Left:* Film dated September 25, 1959 was made before institution of combined therapy. Note the enormously enlarged heart secondary to cor pulmonale. *Center:* Film dated November 18, 1959 was taken 31 days after completion of irradiation therapy (1,700 r depth dose) to the right lung. *Right:* Film dated December 30, 1959 was made 23 days after completion of irradiation (1,700 r depth dose) to the left lung. The return of the heart size to that approximating normal should be noted.

ent. First, significant and at times prolonged periods of tumor regression can be obtained with radiation tumor doses of 2,000 roentgen units or less, thus minimizing the deleterious effects of irradiation on certain normal tissues. For example, one or both lungs containing multiple metastatic lesions may be treated with relatively little risk of producing radiation pneumonitis or fibrosis. Second, recurrent tumors in previously heavily irradiated areas may be re-treated with less danger of producing radiation necrosis. Moreover, combined therapy of the type herein described opens up new avenues for research in the treatment of patients with inoperable cancer, for example, (1) studies of duration of remission and/or survival times of patients with inoperable primary lesions treated with 5-FU and irradiation in tumor doses far in excess of 2,000 roentgen units, using supravoltage as well as orthovoltage techniques; and (2) utilization of analogues of 5-FU—5-fluoro-2′-deoxyuridine (FUDR) and 5-bromo-2′-deoxyuridine (BUDR)—with ionizing irradiation to determine whether or not these compounds might be less toxic than 5-FU. In our investigation to date, the initial response to combined therapy has been impressive. Consequently, a study designed to determine the long-term effects of treatment with 5-FU and irradiation has been initiated.

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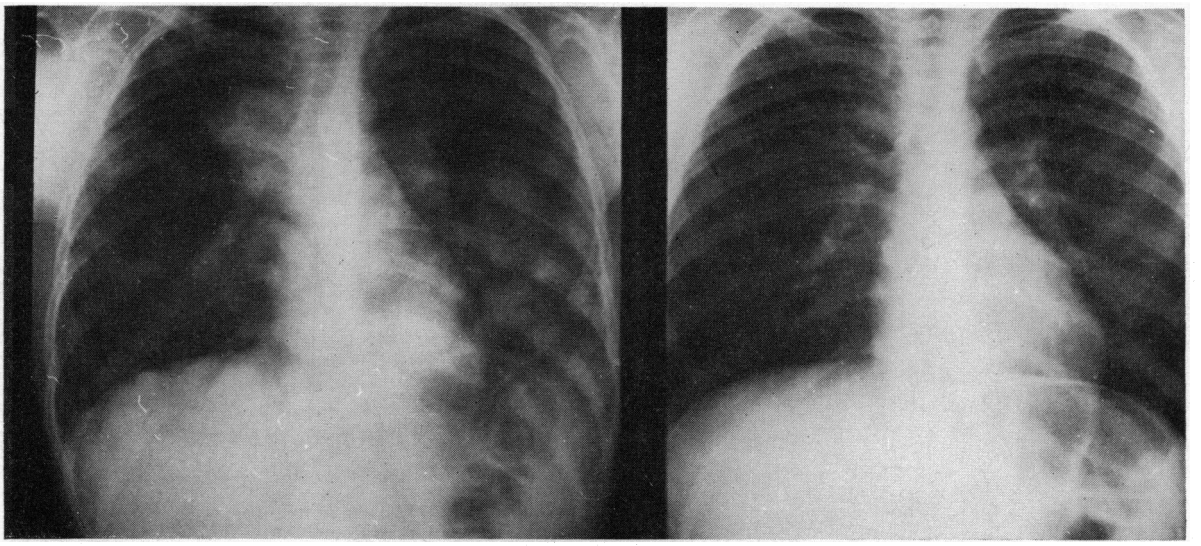

Figure 6.—The patient, a 16-year-old boy, had pulmonary, hilar and mediastinal metastatic lesions from Ewing's sarcoma arising in right calcaneus. *Left:* Film dated May 25, 1960 was taken before combined therapy. *Right:* Film dated June 20, 1960 was made one day after completion of irradiation (1,000 r depth dose to both lungs).

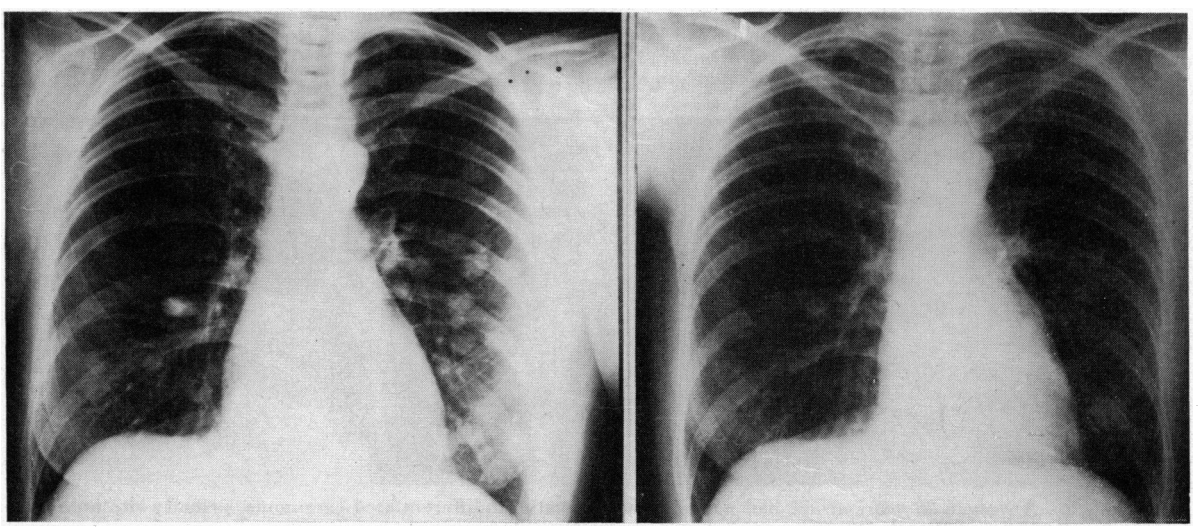

Figure 7.—A woman, 49 years of age, had pulmonary metastasis from adenocystic carcinoma of the salivary gland. *Left:* Film dated February 23, 1960 was before combined therapy was begun. *Right:* Film dated May 17, 1960 was made 43 days after completing a course of irradiation to the left lung (1,700 r depth dose) and 18 days after completion of irradiation to the right lung (1,800 r depth dose).

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